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Application No.: 10/019,049
Inventor: Rosenberg et al.
Reply to Office Action of 13 March 2006
Docket No.: 0480/01221

REMARKS/ARGUMENTS

Claims 4-8 are pending.

Rejection under 35 USC §103

Claims 4-8 are rejected for allegedly being obvious over WO 99/00131 (hereinafter "Krape") in light of Remon et al. Applicants respectfully disagree.

To establish *prima facie* obviousness, the Examiner must show in the prior art some suggestion or motivation to make the claimed invention, a reasonable expectation for success in doing so, and a teaching or suggestion of each Claim element (*See, e.g., In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)). Most inventions arise from a combination of old elements and each element may often be found in the prior art (*In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998)). However, mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole (*Id.* at 1355, 1357). Rather, to establish a *prima facie* case of obviousness based on a combination of elements disclosed in the prior art, the Examiner must articulate the basis on which it concludes that it would have been obvious to make the claimed invention (*Id.*). In practice, this requires that the Examiner "explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious" (*Id.* at 1357-59). This entails consideration of both the "scope and content of the prior art" and "level of ordinary skill in the pertinent art" aspects of the *Graham* test.

Claim 4 recites the following:

A process for producing a solid or semisolid preparation which is substantially free of volatile organic solvent, said preparation comprising paroxetine or one of its physiologically acceptable salts in the form of a molecular dispersion in a pharmaceutically acceptable matrix material which comprises a completely synthetic polymer having a glass transition temperature of >90°C in the anhydrous state,
which process comprises the paroxetine or one of its salts and the matrix material

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being mixed to give a homogeneous melt in an extruder and subsequently being shaped.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art (*See, In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)).

Applicants respectfully assert the cited art references fail to teach all the limitations of the instant claimed invention. The cited art fails to teach at least the following:

- 1) paroxetine or one of its physiologically acceptable salts in the form of a molecular dispersion in a pharmaceutically acceptable matrix material which comprises a completely synthetic polymer having a glass transition temperature of $>90^{\circ}\text{C}$ in the anhydrous state; and
- 2) the paroxetine or one of its salts and the matrix material being mixed to give a homogeneous melt in an extruder and subsequently being shaped.

Accordingly, Applicants respectfully request withdrawal of the 103 rejection and allowance of claim 4-8.

In the Office Action of 13 March 2006, the Examiner asserts the following:

the review article by Remon et al., discloses that the most popular method of forming pellets from a melt is by extrusion (see page 132, left column and first full paragraph; and page 134, left column and first paragraph).

Applicants have reviewed the cited art reference for the subject matter referred to by the Examiner and respectfully submit that the cited art reference fails to teach, suggest or disclose a melt as indicated by the Examiner but in complete contrast instead teaches the preparation of a wet mass. The Examiner is directed to page 132, the sentences bridging the left and right columns which state "... used a continuous granulator to prepare the wet powder mass" and "[d]uring the granulation step the evaporation of the fluid phase should be restricted to a minimum," and to page 134, first sentence, wherein the cited art reference states "... is the shaping of the wet mass into long rods." Accordingly, Applicants respectfully submit that the

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art reference cited by the Examiner does not teach that the most popular method of forming pellets is by melt extrusion, but rather by wet mass extrusion-spheronization.

Moreover, Applicants respectfully assert that one of ordinary skill in the art would have known that melt extrusion and wet mass extrusion-spheronization are two completely separate methods for forming pellets such that there is no motivation to select this reference for combination. Wet mass extrusion-spheronization has the requirement for water and needs an energy intensive and time consuming drying process after extrusion. Melt extrusion on the other hand uses molten binders instead of water and provides for a more uniform dispersion of particles. In view thereof, there is simply no motivation to combine the references.

Therefore, because Remon et al. does not teach "that the most popular method of forming pellet from a melt is extrusion" (Office Action 13 March 2006, page 6) and fails to teach a "melt" as known to one of ordinary skill in the art, Applicants respectfully request withdrawal of the instant rejection for failure to establish *prima facie* obviousness. Favorable action is solicited.

Turning now to Krape, this cited art reference teaches two alternatives for preparing solid state dispersions of paroxetine. First, in the so-called "solution method," the active ingredient is dispersed in a water-soluble carrier by dissolving a physical mixture containing the active ingredient and the pharmaceutically acceptable carrier in a common organic solvent, and then removing the solvent by evaporation. The aforementioned is not a melt process.

The second process is the so-called "fusion" or "melt" process. This process involves contacting a water-soluble pharmaceutically acceptable polymeric carrier with paroxetine free base and heating the mixture to form a molten homogenous melt. Next, the melt contacts hydrogen chloride to form the hydrochloride of paroxetine. Lastly, the melt is cooled to form the solid state dispersion. Applicants respectfully direct the Examiner to page 4, lines 17-24 wherein Krape teaches that the pharmaceutically acceptable carrier has a melting point significantly lower than that of anhydrous paroxetine hydrochloride which allows for the practice of this process at temperatures substantially lower than the melting point of paroxetine hydrochloride.

Because the melting point of anhydrous paroxetine hydrochloride is approximately 118°C, one of ordinary skill in the art would have known that Krape fails to teach, suggest or

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disclose the use a polymer having a glass transition temperature $> 90^{\circ}\text{C}$ in the "fusion" process. The Examples of Krape provide further evidence of the failure to teach, suggest or disclose a polymer having a glass transition temperature $> 90^{\circ}\text{C}$ because whenever the "fusion" process was used, i.e., Examples 1, 14, 15 and 16, PEG-8000, a polymeric carrier which does not have a glass transition temperature of $> 90^{\circ}\text{C}$, was employed. Additionally, and dissimilar to the extrusion of the instant claimed invention's homogeneous melt in an extruder, the aforementioned "fusion" process of Krape occurs in a flask.

Accordingly, Krape fails to teach, suggest or disclose forming the melt in an extruder and requires that the melt is formed with a pharmaceutically acceptable carrier having a melting point significantly lower than that of anhydrous paroxetine hydrochloride.

Consequently, one of ordinary skill in the art would fail to be motivated to combine the wet mass extrusion-spheronization of Remon et al. with the flask formed "fusion" process of Krape with the expectation for success practicing the instant claimed invention.

In light of the aforementioned, the Examiner's rejection appears to be based on an "obvious to try" standard rather than the requisite *Graham* factors. Krape and Remon et al. give no indication of which critical parameters can be modified and provide no direction as to which combination and/or modification of parameters is likely to be successful (*See e.g., In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). Indeed, the Krape specifically teaches that the pharmaceutically acceptable carrier has a melting point significantly lower than that of anhydrous paroxetine hydrochloride is critical, dissimilar to the required $>90^{\circ}\text{C}$ required of instant claim 4. In fact, the experimental examples contained in Krape that use the "fusion" process all use PEG 8000 which does not have a glass transition temperature of $> 90^{\circ}\text{C}$. Further, Remon et al. teaches the criticality of restricting fluid evaporation during granulation of the wet mass extrusion-spheronization process and teaches the benefits of cooling to prevent such evaporation during granulation. Thus, one of ordinary skill in the art would have been lead away from the instant claimed inventions by the combinations and modifications propounded by the Examiner.

In this regard, the Federal Circuit in *In re Fulton* stated that a cited art reference that

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criticizes, discredits, or otherwise discourages the solution claimed teaches away (391 F.3d 1195, 1201 (Fed. Cir. 2004)). Indeed, for example, Krape is replete with instructions wherein the use of paroxetine or one of its physiologically acceptable salts in the form of a molecular dispersion in a pharmaceutically acceptable matrix material which comprises a completely synthetic polymer having a glass transition temperature of $>90^{\circ}\text{C}$ in the anhydrous state, is discouraged or discredited (e.g. Examples 1, 14, 15 and 16) and as such, because the this cited art reference teaches away from the instant invention, the Examiner's rejection using Krape in combination with Remon et al. is improper. Because it is improper to combine references where the references teach away from their combination, the Examiner is in error in applying Krape and Remon et al. in an obviousness rejection (See e.g., *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983)).

Additionally, known compositions do not render an invention obvious simply because they could be combined; to establish a *prima facie* case of obviousness, the Examiner must provide a rationale for said combination. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the cited art also suggests the desirability of the combination (*In re Mills*, 916 F.2d 680 (Fed. Cir. 1990)). Moreover, the question regarding whether to combine references must be complete. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be disregarded¹. Applicants assert that there is no motivation to combine the cited art references the Examiner has used as a basis for the § 103 rejection. Referring again to the facts described above wherein the "fusion" process teachings and Example data of Krape do not provide motivation to use it to practice the instant invention. More specifically, one of ordinary

¹ See, e.g., *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an essential component of an obviousness holding") (quoting *C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998)); *In re Dembitz*, 175 F.3d 994, 999 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Dance*, 160 F.3d 1339, 1343 (Fed. Cir. 1998) ("there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant"); *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988) ("teachings of references can be combined only if there is some suggestion or incentive to do so.") (emphasis in original) (quoting *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577 (Fed. Cir. 1984)).

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skill in the art would not have been motivated to combine the lower temperature flask "fusion" process of Krape with the preferably cooled wet mass extrusion-spheronization of Remon et al. with the expectation for success.

In accordance with the above, the prior art must also provide a reasonable expectation of success (*See e.g., Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003)). "A showing of obviousness requires a motivation or suggestion to combine or modify prior art references, coupled with a reasonable expectation of success). Additionally, the court in *In re O'Farrell* held the claimed method would have been obvious over the prior art relied upon because, in part, there was evidence suggesting the modification would be successful. Alternatively, evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness (*In re Rinehart*, 531 F.2d 1048 (CCPA 1976) (*See also*, MPEP 2143.02)). In accordance with that stated above, the use of a preferably cooled wet mass extrusion-spheronization combined with the low temperature flask "fusion" process fails to provide the required reasonable expectation of success. Consequently, assuming *arguendo* that one of ordinary skill in the would have been motivated to combine Krape and Remon et al., this combination would still have been improper because there would have been no expectation of success for practicing the instant invention.

In sum, because of the above, Applicants believe the Examiner has engaged in prohibited hindsight reasoning to arrive at the present invention. To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher (*W. E. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)).

Accordingly, because Krape and Remon et al. fail to teach, suggest or disclose to instant claimed invention, alone or in combination, and in fact teach away from the use of paroxetine or one of its physiologically acceptable salts in the form of a molecular dispersion in a pharmaceutically acceptable matrix material which comprises a completely synthetic polymer having a glass transition temperature of $>90^{\circ}\text{C}$ in the anhydrous state, and the paroxetine or one

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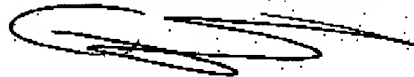
of its salts and the matrix material being mixed to give a homogeneous melt in an extruder and subsequently being shaped, these cited art references cannot be combined in the manner suggested by to Examiner to successfully practice the instant claimed invention. Withdrawal of the Examiner's rejection is hereby respectfully requested.

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Conclusion

Applicants respectfully submit that the present application is in condition for allowance, which action is courteously requested. Please charge the one-month extension fee to the credit card listed on the enclosed Form PTO-2038. Please charge any shortage in fees due in connection with the filing of this paper to Deposit Account 14.1437. Please credit any excess fees to such account.

Respectfully submitted,



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